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Convenient Preparation of Furanoeremophilane and Menthofuran[1)]

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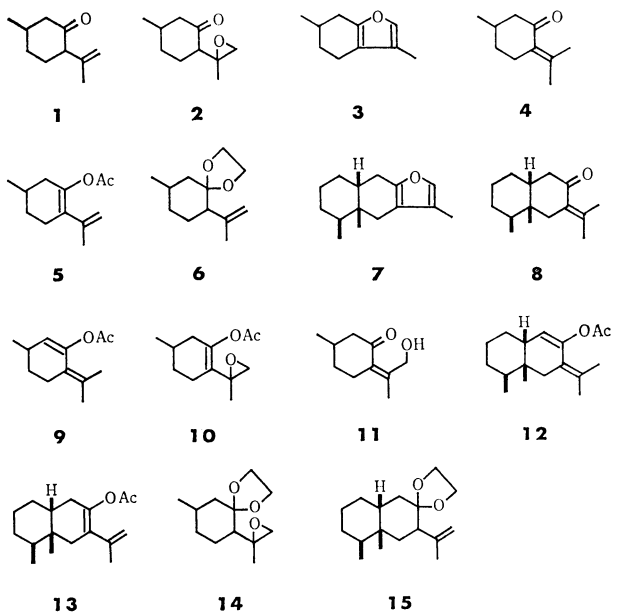
Synopsis. Pulegone was transformed into isopulegone enol acetate or isopulegone ethylene acetal, which was treated with *m*-chloroperbenzoic acid and then with acid to give menthofuran. Fukinone was converted into furanoeremophilane by the same procedure.

It has been reported that oxidation of isopulegone (**1**) with perbenzoic acid and subsequent treatment of a keto epoxide (**2**) with hot dilute acid give menthofuran (**3**) in 13% yield.[2)] The present paper deals with a convenient preparation of **3** from pulegone (**4**) *via* isopulegone enol acetate (**5**) or isopulegone ethylene acetal (**6**). Although the preparation is similar to that reported, the yield was much improved. Preparation of furanoeremophilane (**7**) from fukinone (**8**) by the same procedure is described.

Enol acetylation of pulegone (**4**) gave a mixture of **5** and pulegone enol acetate (**9**) quantitatively in a *ca.* 5:3 ratio. Enol acetate (**5**) with isopropenyl double bond was isolated in 59% yield, epoxidized with *m*-chloroperbenzoic acid in the presence of phosphate buffer solution (pH 7.2),[3)] and the reaction mixture was treated with *p*-toluenesulfonic acid to afford menthofuran (**3**)[4)] in 68% yield. The reaction of **5** to form **3**[1,5)] may proceed through an epoxide (**10**) and (or) a hydroxy ketone (**11**)[6)] as an intermediate. However, no information could be obtained about the intermediate due to its labile nature.

Similarly, fukinone (**8**)[7)] was enol acetylated to give two enol acetates **12** and **13** in 27% and 40% yields, respectively. The enol acetate (**13**) was treated successively with *m*-chloroperbenzoic acid and *p*-toluenesulfonic acid to afford furanoeremophilane (**7**)[8)] in 42% yield.



Acetalization of pulegone (**4**) proceeded quantitatively to give **6**. Epoxidation of **6** with *m*-chloroperbenzoic acid gave an epoxide (**14**) in 89% yield showing two peaks in a *ca.* 2:1 ratio on GLC examination. The major epoxide was separated by means of preparative TLC and converted into menthofuran (**3**) by acid treatment (2 M hydrochloric acid–pentane).[9)] When the reaction was carried out without separation of the intermediates **6** and **14**, **3** was obtained from **4** in 90% yield.

An ethylene acetal (**15**) with terminal double bond was formed as the sole product on acetalization of fukinone (**8**). Treatment of **15** with peroxy acid and then with acid gave furanoeremophilane (**7**) in 74% yield from **15**.

These two methods are useful for the synthesis of 3-methylfuran derivatives from α-isopropylidene ketones.

Experimental

UV spectra were measured on a Hitachi 124 spectrophotometer, and high resolution mass (MS) spectra on a JEOL JMS-D300 spectrometer. Other details are the same as described in a previous paper.[10)]

Enol Acetylation of Pulegone (4). A mixture of **4** (3.60 g), isopropenyl acetate (4.17 g), and *p*-toluenesulfonic acid (0.5 g) was stirred under nitrogen at room temperature for 15 h. The reaction mixture was passed through a column of silica gel (100 g). An excess of isopropenyl acetate was eluted with pentane. Elution with pentane–ether (50:1) afforded isopulegone enol acetate (**5**; 2.69 g; yield 59%), an oil (one spot on TLC), bp 74.5—77 °C/533 Pa; IR (neat) 1760, 1635, and 900 cm^{-1}; UV_{max} (EtOH) 223 nm (ε 5700); NMR (CS_2) δ 0.88 (3H, d, J=6 Hz), 1.74 (3H, d-like, J=1.5 Hz), 1.92 (3H, s), and 4.73 (2H, m); NMR (CCl_4) δ 1.03 (3H, d, J=6 Hz), 1.78 (3H, d-like, J=1.5 Hz), 1.98 (3H, s), and 4.77 (2H, m). Found: *m/e* 194.1308. Calcd for $C_{12}H_{18}O_2$: M, 194.1307. Successive elution with the same solvents gave pulegone enol acetate (**9**; 1.50 g; yield 33%), an oil (one spot on TLC); IR (neat) 1760 cm^{-1}; UV_{max} (EtOH) 241 nm (ε 3400); NMR (CCl_4) δ 1.00 (3H, d, J=6.5 Hz), 1.74 (3H, br. s), 1.82 (3H, br. s), 2.00 (3H, s), and 5.07 (1H, d, J=3 Hz). Found: *m/e* 194.1278. Calcd for $C_{12}H_{18}O_2$: M, 194.1307.

Menthofuran (3) from Isopulegone Enol Acetate (5). A buffer solution (pH 7.2; 20 ml; prepared from KH_2PO_4–NaOH–H_2O) and *m*-chloroperbenzoic acid (2.3 g) in ether (30 ml) were added to a solution of **5** (250 mg) in ether (10 ml) at 0 °C, and the mixture was stirred for 30 min. The organic layer was washed with a 10% aqueous sodium thiosulfate solution and treated with *p*-toluenesulfonic acid (30 mg) in ether at room temperature for 2 min. The ethereal solution was washed with a 5% sodium hydroxide solution and brine, dried ($MgSO_4$) and evaporated, giving a residue which was chromatographed (silica gel, 5 g; elution with pentane) to

afford menthofuran (**3**; 132 mg; yield 68%), an oil (one spot on TLC); IR (neat) 1635 and 1560 cm^{-1}; NMR (CS_2) δ 1.09 (3H, d, J=5.5 Hz), 1.85 (3H, d, J=2 Hz), and 6.84 (1H, m); NMR (CCl_4) δ 1.06 (3H, d, J=5.5 Hz), 1.86 (3H, d, J=2 Hz), and 6.88 (1H, m). Found: *m/e* 150.1032. Calcd for $C_{10}H_{14}O$: M, 150.1045.

Furanoeremophilane (7) from Fukinone (8). Fukinone (**8**; 351 mg) was treated with isopropenyl acetate (300 mg) in the presence of *p*-toluenesulfonic acid (50 mg) under nitrogen with stirring at room temperature for 15 h. The reaction mixture was passed through a column of silica gel (10 g). An excess of isopropenyl acetate was eluted with pentane. Elution with pentane–ether (25: 1) gave an enol acetate (**13**; 164 mg; yield 40%), an oil (one spot on TLC); IR (neat) 1760 and 895 cm^{-1}; NMR (CS_2) δ 0.88 (3H, d, J=6.5 Hz), 0.91 (3H, s), 1.73 (3H, d-like, J=1.5 Hz), 1.92 (3H, s), 4.68 (1H, m), and 4.77 (1H, m); MS *m/e* 262 (M^+). Successive elution with the same solvent mixture gave another enol acetate (**12**; 114 mg; yield 27%), an oil (one spot on TLC); IR (neat) 1760 cm^{-1}; NMR (CS_2) δ 0.70 (3H, d, J=6 Hz), 0.90 (3H, s), 1.74 (3H, br s), 1.81 (3H, br s), 2.00 (3H, s), and 4.80 (1H, d, J=3 Hz); MS *m/e* 262 (M^+).

The enol acetate (**13**; 85 mg) was dissolved in ether (10 ml), and treated with *m*-chloroperbenzoic acid (650 mg) in ether (50 ml) at 0 °C for 1 h with stirring in the presence of the phosphate buffer solution (10 ml; *vide supra*). The organic layer was treated as described above (including the treatment with *p*-toluenesulfonic acid, 10 mg) to give a residue which was chromatographed (silica gel, 5 g; elution with pentane) to give furanoeremophilane (**7**; 30 mg; yield 42%). The IR and NMR spectra were identical with those of an authentic **7**.[8]

Acetalization of Pulegone (4). Ethylene glycol (2.5 ml) and *p*-toluenesulfonic acid (100 mg) were added to a solution of **4** (2.24 g) in benzene (20 ml) and the mixture was refluxed under nitrogen for 7.5 h using a Dean-Stark water separator. The organic layer was washed with aqueous sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and evaporated, giving a residue. This was passed through a column of silica gel (30 g) [elution with hexane–ether (20: 1)] to give isopulegone ethylene acetal (**6**; 2.84 g; yield 98%), an oil showing one spot on TLC and one peak at R_t=8.7 min on GLC examination [column, SP-1000 (10%), 3(mm)×2(m); 160 °C; N_2 flow rate, 40 ml/min]; IR (neat) 1640 and 890 cm^{-1}; NMR (CCl_4) δ 0.90 (3H, d, J=6 Hz), 1.74 (3H, m), 3.78 (4H, br s), and 4.74 (2H, m). Found: *m/e* 196.1455. Calcd for $C_{12}H_{20}O_2$: M, 196.1464.

Menthofuran (3) from Isopulegone Ethylene Acetal (6). A solution of *m*-chloroperbenzoic acid (266 mg) in ether (20 ml) was added to **6** (304 mg) in ether (10 ml) at 0 °C, and the mixture was stirred for 15 h. The ethereal solution was washed with a 10% aqueous sodium thiosulfate solution, aqueous sodium hydroxide solution and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure (at below 20 °C) to give a residue which was chromatographed on a column of Florisil (5 g). Elution with pentane–ether (5: 1) gave an epoxide (**14**; 294 mg; yield 89%) as an oil. The epoxide (**14**) showed two spots on TLC and two peaks at R_t=10.1 min (a major epoxide) and R_t=10.8 min (a minor epoxide) in a ratio of *ca.* 2: 1 on GLC examination under the same conditions as described above. Epoxide (**14**) was further chromatographed [silica gel, 3 g; elution with pentane–ether (5: 1)] to afford the major epoxide, an oil (one spot on TLC); NMR (CCl_4) δ 0.89 (3H, d, J=6 Hz), 1.19 (3H, s), 2.46 and 2.67 (each 1H, J=6 Hz, CH_2 in an oxirane ring), and 3.86 (4H, m, O–CH_2–CH_2–O). Found; C, 68.05; H, 9.58%. Calcd for $C_{12}H_{20}O_3$: C, 67.89: H, 9.50%. The minor epoxide could not be obtained as a pure sample.

To this major epoxide (1024 mg) in pentane (15 ml) was added 2 M hydrochloric acid (15 ml), and the mixture was stirred at room temperature for 1.5 h. The pentane layer was separated and the aqueous layer was further extracted with pentane (total 50 ml). A combined pentane solution was washed with aqueous sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and evaporated (at below 28 °C), giving a residue which was chromatographed on a column of Florisil (5 g). Elution with pentane afforded menthofuran (**3**; 674 mg) in 93% yield, identical (IR, NMR, MS, and TLC) with the authentic sample (*vide supra*).

Acetalization of Fukinone (8). Fukinone (160 mg) in benzene (7 ml) was acetalized with ethylene glycol (1 ml) in the presence of *p*-toluenesulfonic acid (30 mg; in benzene, 5 ml) under reflux (12 h) using a Dean-Stark water separator. After the usual work-up, the residue was chromatographed [silica gel, 10 g; elution with hexane–ether (20: 1)] to give an ethylene acetal (**15**; 112 mg) in 58% yield, an oil (one spot on TLC); IR (neat) 1635 and 890 cm^{-1}; NMR (CCl_4) δ 0.88 (3H, d, J=5 Hz), 0.97 (3H, s), 1.78 (3H, m), 3.78 (4H, m), and 4.50 (2H, m); MS *m/e* 264 (M^+). Further elution with the same solvents gave fukinone.

Furanoeremophilane (7) from the Ethylene Acetal (15). A solution of **15** (44 mg) in ether (10 ml) was epoxidized with *m*-chloroperbenzoic acid (55 mg; in ether, 20 ml) at 0 °C (4.5 h). The ether solution was washed with a 10% aqueous sodium thiosulfate solution, a 5% sodium hydroxide solution, and brine, and then treated with 2M hydrochloric acid (10 ml) under nitrogen at room temperature for 20 min. The ether layer was separated and the aqueous layer was further extracted with ether (total 20 ml). The combined ether solution was treated as usual to give a residue which was chromatographed on a column of silica gel (2 g). Elution with pentane afforded furanoeremophilane (**7**; 27 mg; yield 74%), identical with the authentic specimen.[8]

References

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